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EXAMINER	
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1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/627,556	LEDBETTER ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58,61-79 and 82-109* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-58, 61-79 and 82-109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-58, 61-79 and 82-109 are all the pending claims for this application.

2. Claims 59 and 60 were cancelled and Claims 3, 50, 53 and 54 were amended in the Response of 6/8/07.

3. Claims 1-58, 61-79 and 82-109 are all the pending claims under examination.

4. Applicants arguments have not overcome all of the outstanding rejections. This action is FINAL.

Information Disclosure Statement

5. The copy of the BBBB reference (Damle et al.. Eur. J. Immunol. 21:1277-1282 (1991); cited in the IDS of 7/2/04) provided with the Response of 6/8/07 has been considered and entered and is cited on the attached PTO 892 form.

Withdrawal of Objections

Specification

6. The objections to the disclosure are withdrawn:

a) The amendment of the specification to insert SEQ ID NOS is entered by way of the substitute specification filed 6/8/07.

b) The amendment of the specification to delete the embedded hyperlink is entered by way of the substitute specification filed 6/8/07.

c) The amendment of the specification to properly identify trademarks throughout the specification, e.g., Panorex®, Antilfa®, Zevalin® (see p. 31 for example), is entered by way of the substitute specification filed 6/8/07.

c) The amendment of the specification to include a brief description of the drawings for Figure 6A and B and Figure 19A, B and C, is entered by way of the substitute specification filed 6/8/07.

Claim Objections

7. The objection to Claims 57 and 59, and Claims 58 and 60 for reciting duplicate subject matter is withdrawn in view of cancelled Claims 59 and 60.

8. The objection to Claim 50 for omitting to insert a comma between "shiga toxin" and "Pseudomonas Exotoxin A" is withdrawn in view of the amended claim.

9. The objection to Claims 53 and 54 for failing to identify the sequences by SEQ ID NO. is withdrawn in view of the amended claims.

Withdrawal of Rejections

Claims - 35 USC § 112, second paragraph

10. The rejection of Claim 3 in lacking antecedent basis for the limitation "the one or more amino acid substitution or deletion in said heavy chain variable region" is withdrawn in view of the amended claim to recite "the amino acid", and further in view of Applicants' comments on pp. 15-16 of the Response of 6/8/07.

11. The rejection of Claims 14-16 for reciting "an increased recombinant expression or stability" is withdrawn in view of Applicants' allegations on p. 16 of the Response of 6/8/07.

12. The rejection of Claims 29 and 30 for reciting that the single chain Fv is a "hd37 single chain fv, 2h7 single chain fv, g28-1 single chain fv, and 4.4.220 single chain fv" is withdrawn in view of Applicants allegations on p. 16 of the Response of 6/8/07.

13. The rejection of Claim 30 for reciting "FC2-2, UCHL-1, 5B9, L6, 10A8, 2e12, 40.2.36, G19-4, 1D8" is withdrawn in view of Applicants allegations on pp. 16-17 of the Response of 6/8/07.

Further as regards the withdrawal of the rejections under sections 12 and 13 supra, Applicants admit on the record under section VI, p. 22 of the Response "*that the claims are directed to proteins having binding domains comprising variable sequences that are based on the sequences of the indicated hybridomas, and not to a hyrbidoma producing the antibody having the altered variable region.*"

Claims - 35 USC § 112, first paragraph

Enablement

14. The rejection of Claims 1-58, 61-79 and 81-109 (section 15, subsection a of the Office Action of 12/8/07) under 35 U.S.C. 112, first paragraph, in lacking enablement for a binding domain-immunoglobulin fusion protein comprising a binding domain polypeptide which comprises *only* a light chain variable domain *or only* a heavy variable domain is withdrawn.

The rejection is rendered moot for cancelled Claims 59 and 60.

Applicants' admission on the record under section VI (a), pp. 18-19 of the Response of 6/8/07 "*that Claims 1 and 77 encompass a protein having at least a heavy chain variable region and a protein having both a heavy chain variable region and a light chain region"* and *"the claims do not recite a protein having only a light chain variable region"* overcomes the rejection for Claims 1-58, 61-79, and 81-109.

Applicants' discussion on p. 19 of the Response about the subset of functional antibodies having only a heavy chain variable region (e.g., camelid, sharks, etc.) is acknowledged but irrelevant in view of the admission of record above. Further, Applicants have not explained how the overall structures for the subset of single variable domain antibodies especially the hinge region is distinct and separate from the hinge of an IgG, for example, in the references cited in the Response (Nutall et al., Curr. Pharm. Biotechnol. 1:253-263 (2000); Muyldermans, J. Biotechnol. 74:277-302 (2001), Abstract). Nevertheless, Applicants admission of record that the claims are not drawn to camelid-like (or shark- or llama-like) antibodies renders the rejection moot.

Applicants' provide a single art reference (Ward et al., Nature 341:544-546 (1989); Abstract) describing a single domain antibody retaining antigen- binding affinity. Applicants have not demonstrated that this same method of producing a single domain antibody could be reliably, predictably and reproducibly practiced using just any variable domain from just any antibody. Applicants have not demonstrated the universality of producing a fully functional single domain antibody that meets all of the limitations of the instant claims. Nevertheless, Applicants admission of record that the claims are not drawn to single domain antibodies renders the rejection moot.

15. The rejection of Claims 29, 30 and 83-108 (section 15, subsection b in the Office Action of 12/8/06) under 35 U.S.C. 112, first paragraph, in lacking enablement for a single chain antibody having antigen binding specificity for any antigen or any scFv having antigen binding specificity for any antigen and comprising *any* amino acid substitution or deletion in any one or more positions 9, 10, 11, 12, 108, 110 and 112 for the VH region and/or *any* amino acid substitution or deletion in one or more of positions 12, 80, 81, 83, 105, 106 and 107 for the VL region is withdrawn.

Applicants' amendment of the specification to include SEQ ID NOS for specific embodiments for the scFvs described and encompassed by the claims is considered persuasive. The replacement specification only now allows one of ordinary skill in the art the ability to identify the inventive modified scFvs, for example, 2H7 (SEQ ID NOS:21-28); HD37 (SEQ ID NOS:387-392), G28 (SEQ ID NOS:309-314), FC2-2 (SEQ ID NOS:333338), UCHL-1 (SEQ ID NOS:347-352), 5B9 (SEQ ID NOS:116-123), L6

(SEQ ID NOS:403-408), 10A8 (SEQ ID NOS:43-48), 2E12 (SEQ ID NOS:37-42), G19-4 (SEQ ID NOS:443-444), 1D8 (SEQ ID NOS:100-105) and 4.4.220 (SEQ ID NOS:32-36). The replacement specification only now allows one of ordinary skill in the art the ability to cross-reference the inventive, modified scFv embodiments with the biological data shown in the specification in order to determine whether the modified scFvs actually possess functional characteristics that meet the limitations of the generic claims from which they depend.

Rejections Maintained

Claims - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. The rejection of Claim 13 for the recitation "des-leucine" is maintained. Applicants' allegations on p. 16 of the Response have been considered but are not persuasive. Applicants state that the term is "frequently used in the art" as supported by example of the copy of the reference article J. Biol. Chem. 242:555-557 (1967). No copy of the reference article appears to have been received by the Office with the Response of 6/8/07.

Claims - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Biological Deposit Requirement

17. The rejection of Claims 29, 30 and 83-108 under 35 U.S.C. § 112, first paragraph, because the specification does not indicate that biological deposits have been made for the hybridoma cell lines HD37, G28-1, 4.4.220, Fc2-2, UCHL-1, 5B9, L6, 10A8, 2e12, 40.2.36 or G19-4 is maintained.

Applicants' allegations on p. 17 of the Response have been considered but are not persuasive. Applicants allege "the sequence of the hybridomas are set out as follows: 2H7 (SEQ ID NOS:21-28); HD37 (SEQ ID NOS:387-392), G28 (SEQ ID NOS:309-314), FC2-2 (SEQ ID NOS:333338), UCHL-1 (SEQ ID NOS:347-352), 5B9 (SEQ ID NOS:116-123), L6 (SEQ ID NOS:403-408), 10A8 (SEQ ID NOS:43-48), 2E12 (SEQ ID NOS:37-42), G19-4 (SEQ ID NOS:443-444), 1D8 (SEQ ID NOS:100-105) and 4.4.220 (SEQ ID NOS:32-36)."

Based on closer inspection, the sequences referred to by Applicants are for engineered scFvs, which are produced from the parent antibodies secreted by the hybridomas HD37, G28-1, 4.4.220, Fc2-2, UCHL-1, 5B9, L6, 10A8, 2e12, 40.2.36 or G19-4. Absent evidence to the contrary, Applicants have not identified where one of ordinary skill in the art could identify the sequence information in the specification for any one of the parent antibodies produced from the respective hybridoma cell lines.

Unless the specification discloses sequence information for each of the parent antibodies produced by the respective hybridomas, the rejection is maintained for claims encompassing the hybridomas that do not meet the deposit requirements under 112, first paragraph.

Scope of Enablement

18. The rejection of Claims 1-28, 31-58, 61-79, 81, 82 and 109 (section 15, subsection b in the Office Action of 12/8/06) under 35 U.S.C. 112, first paragraph, in lacking enablement for a single chain antibody having antigen binding specificity for *any* antigen or a scFv having antigen binding specificity for *any* antigen and where the single chain antibody or scFv comprise *any* amino acid substitution or deletion in any one or more positions 9, 10, 11, 12, 108, 110 and 112 for the VH region and/or *any* amino acid substitution or deletion in one or more of positions 12, 80, 81, 83, 105, 106 and 107 for the VL region is maintained.

Applicants' allegations on pp. 20-21 have been considered but are not found persuasive. Applicants allege that because the specification teaches: VH substitution of position 11 with des-leucine (p. 20), [346] of the specification describes several references showing methods for engineering framework and CDR residues (p. 20), WO92/01787 and WO98/02462 describe residues of V domains in which substitutions can be made (p. 20), and methods for measuring functional properties of antibodies, the instant claims are fully enabled.

Applicants have not addressed any of the references cited in the Office Action to substantiate the Examiner's position that amino acid substitutions in proteins, more especially framework and CDR residues for antibodies, can dramatically effect or reduce the function of the antibody (see Rudikoff).

Applicants have not addressed the *predictability* prong of the WANDS test for making antibodies meeting all of the limitation of the claims. The skilled artisan would have been required to identify candidate VH and VL domains from any antibody recognizing any antigen, to have modified the amino acid residues in the recited positions of the VH and VL domains, and combined the modified VH and VL domains in order to have produced a single chain antibody or scFv capable of recognizing the antigen, having increased expression or stability, and having at least one immunological activity. At this point, one skilled in the art would need to have produced and expressed the antibodies, assessed binding activity against the parent antibody, and then finally performed any bioassays to measure antigen binding characteristics (e.g., binding specificity, equilibrium dissociation constant (K.sub.D), dissociation and association rates (K.sub.off and K.sub.on respectively), binding affinity and/or avidity). The technology to perform these experiments was available at the time of application filing, but one of ordinary skill in the art could not have predicted from the universe of single chain antibodies and scFv antibodies directed against the universe of antigens which one or combination of CDR and/or framework modifications in the VH and/or VL would generate a single chain antibody or scFv having antigen binding specificity for *any* antigen, increased expression or solubility *and* at least one immunological activity.

Therefore, in view of the lack of examples and lack of predictability associated with regard to producing the myriad single chain antibodies and scFvs which meet all of the claim limitations, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

19. The rejection of Claims 29, 30 and 83-108 (section 15, subsection c in the Office Action of 12/8/06) under 35 U.S.C. 112, first paragraph, in lacking enablement for the hybridoma cell lines, 2H7, HD37, G28-1, 4.4.220, Fc2-2, UCHL-1, 5B9, L6, 10A8, 2e12, 40.2.36, 1D8 or G19-4, is maintained for the reasons set forth under the discussion for "Biological Deposit Requirement".

Claims - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. The rejection of Claims 1-12, 14-23, 25-28, 31-47, 52-55, 57, 58, 61-63, 65, 68, 69, 71, 72, 76-79 and 109 under 35 U.S.C. 103(a) as being unpatentable over Shan et al (J. Immunol. 162:6589-6595 (1999); hereinafter referred to as "Shan"; cited in the IDS of 7/2/04) in view of Pluckthun et al. (USPN 6,815,540; published 11/9/2004; filed 1/15/1999; hereinafter referred to as "Pluckthun") is maintained.

Applicants' allegations on pp. 22-24 of the Response of 6/8/07 have been considered but are not persuasive. Applicants allege Shan neither discloses nor suggests structural modifications of the variable region to obtain increased expression and Pluckthun teaches changing residues 84, 87 and/or 89 imparts improved properties (col. 11, lines 20-59). One of skill in the art would not be motivated to modify a VH at position 11 when Pluckthun teaches toward other modifications.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention

where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992) and *KSR Internt'l. Co. v. Teleflex Inc.* (82 USPQ2d 1385 (2007).

In this case, Pluckthun discloses an example of a scFv mutant at VH position 11 (Flu6 (L11D/V84D) (FIG. 3B lane 7, 8) that yielded about 0.25 mg per liter of protein whereas the wt scFv antibody did not give any soluble protein. In the passage of Pluckthun cited by Applicants (col. 11, lines 20-59), Plucktun specifically discloses "substituting leu at position 11 in the VH to aspartic acid changes the i/s ratio to more soluble protein but still this effect is not very dramatic". The instant generic claims are not limited by any amount to which the increased expression or stability of the protein must be achieved for the substitution or deletion of position 11 in the VH domain relative to the parent antibody, and yet still retain antigen binding and possess at least one immunological activity.

Shan teaches that the scFv-Ig constructs are amenable to further structural modifications (p. 6954, Col. 2), and the modifications taught by Pluckthun would read on a modified construct for producing increased expression and stability of the scFv-Ig of Shan. Pluckthun discloses the amino acid positions that are critical and amenable to substitution (or deletion) in a construct encoding scFvs like those constructs taught by Shan. Shan is not limited to the kind or extent of the modification and Pluckthun

provides the motivation to modify the construct of Shan without compromising the biological properties of the resulting antibody.

21. The rejection of Claims 1, 56, 65 and 70-72 under 35 U.S.C. 103(a) as being unpatentable over Shan in view of Pluckthun as applied to claim 1 above, and further in view of Bodmer et al. (USPN 5,677,425; published 10/14/1997; hereinafter referred to as "Bodmer"; cited in the IDS of 12/22/04) is maintained.

Applicants' allegations on pp. 24-25 of the Response have been considered but are not persuasive. Applicants allege that Shan and Pluckthun do not provide motivation to produce a scFv with a modification at position 11 of the VH and that Bodmer does not rectify this deficiency.

The Examiner's response to Applicants allegations for Shan and Pluckthun are set forth supra, and where each reference discloses modifications for scFvs, and Pluckthun specifically discloses increased yield by the specific substitution at position 11 of VH, one skilled in the art could readily have further modified the construct of Shan in view of Pluckthun and Bodmer, because Bodmer teaches constant regions, cysteine-altered hinges and humanized antibodies, which would not effect the product yield of the scFvs of Shan and Plucktun.

22. The rejection of Claims 1, 63, 66 and 82 under 35 U.S.C. 103(a) as being unpatentable over Shan in view of Pluckthun as applied to claims 1 and 77 above, and further in view of Bodmer and Morrison et al. (USPN 6,284,536; published 9/4/2001;

filed 8/11/98; hereinafter referred to as "Morrison"; cited in the IDS of 3/21/05) is maintained.

Applicants' allegations on pp. 25-26 of the Response have been considered but are not persuasive. Applicants allege that Shan, Pluckthun and Bodmer do not provide motivation to produce a scFv with a modification at position 11 of the VH and that Morrison does not rectify this deficiency.

The Examiner's response to Applicants allegations for Shan, Pluckthun and Bodmer are set forth supra, and where each reference discloses modifications for scFvs, and Pluckthun specifically discloses increased yield by the specific substitution at position 11 of VH, one skilled in the art could readily have further modified the construct of Shan in view of Pluckthun, Bodmer and Morrison, because Morrison teaches modified antibodies having IgA regions, which would not effect the product yield of the scFvs of Shan in view of Plucktun and Bodmer.

23. The rejection of Claims 1, 64, 67 and 73-75, 77 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shan in view of Pluckthun as applied to claims 1 and 77 above, and further in view of Roux et al. (J. Immunol. 161:4083-4090 (1998); hereinafter referred to as "Roux") is maintained.

Applicants' allegations on pp. 26-27 of the Response have been considered but are not persuasive. Applicants allege that Shan and Pluckthun do not provide motivation to produce a scFv with a modification at position 11 of the VH and that Roux does not rectify this deficiency.

The Examiner's response to Applicants allegations for Shan and Pluckthun are set forth supra, and where each reference discloses modifications for scFvs, and Pluckthun specifically discloses increased yield by the specific substitution at position 11 of VH, one skilled in the art could readily have further modified the construct of Shan in view of Pluckthun and Roux, because Roux teaches modified antibodies having IgE and IgG1 hinge regions and praline-substituted cysteine residues in hinges, which would not effect the product yield of the scFvs of Shan in view of Pluckthun.

Conclusion

24. No claims are allowed.

25. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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